REMARKS

Claims 1-9 are pending and under consideration in the instant application. With the instant Amendment, Claims 1 and 5 are amended. A marked-up version of the amended claims is attached hereto as Exhibit A. Thus, after entry of the instant amendment Claims 1-9 are pending and under consideration. For the PTO's convenience, a clean copy of pending Claims 1-9 is attached hereto as Exhibit B.

I. THE AMENDMENT OF THE CLAIMS

Claims 1 and 5 have been amended to correct minor errors in claim language. As the amendments to the Claims 1 and 5 are fully supported, for example, by Claims 1 and 5 as originally filed, they do not constitute new matter. Entry thereof is therefore respectfully requested.

II. THE REJECTIONS UNDER 35 U.S.C. § 103

Claims 1, 2, 4, 5 and 9 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over a combination of U.S. Patent No. 5,538,848 ("Livak") in view of U.S. Patent No. 5,882,857 ("Western"). Claims 3 and 6-8 stand rejected as allegedly being unpatentable over a combination of Livak and Western. Applicants traverse the rejections on the grounds that neither Livak nor Western, alone or in any combination, teaches or suggests each and every element of Claims 1-9 and that the PTO has failed to cite any reasonable expectation of success for practicing the asserted combination of Livak and Western.

A. The Legal Standard of *Prima Facie* Obviousness

To reject claims in an application under 35 U.S.C. § 103, the Patent Office bears the initial burden of establishing a *prima facie* case of obviousness. *In re Bell*, 26 USPQ2d 1529, 1530 (Fed. Cir. 1993); MPEP § 2142. In the absence of establishing a proper *prima facie* case of obviousness, applicants who comply with the other statutory requirements are entitled to a patent. *In re Oetiker*, 24 USPQ2d. 1443, 1444 (Fed. Cir. 1992).

In order to establish *prima facie* obviousness, three basic criteria must be met. First, the prior art must provide one of ordinary skill in the art with a suggestion or motivation to modify or combine the teachings of the references relied upon by the PTO to arrive at the claimed invention. When an obviousness determination relies on one reference, there must be suggestion or motivation to modify the teaching of the reference in the manner suggested

by the PTO. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985). Alternatively, when an obviousness determination relies on a combination of two or more references, there must be some suggestion or motivation to combine the references. *WMS Gaming Inc. v. International Game Technology*, 51 USPQ2d 1385, 1397 (Fed. Cir. 1999). The suggestion or motivation to combine the references generally arises in the references themselves, but may also be inferred from the nature of the problem or occasionally from the knowledge of those of ordinary skill in the art. *See id.* The mere fact that references *could* be modified or combined does not render the resultant modification or combination obvious unless the prior art also suggests the desirability of the modification or combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); MPEP § 2143.01.

Second, the prior art must provide one of ordinary skill in the art with a reasonable expectation of success. Thus, the skilled artisan, in light of the teachings of the prior art, must have a reasonable expectation that the modification or combination suggested by the PTO would succeed. *In re Dow*, 5 USPQ2d 1529, 1531-32 (Fed. Cir. 1988).

Third, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. *In re Gartside* , 53 USPQ2d 1769 (Fed. Cir. 2000). The teaching or suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, not Applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). If *any one* of these criteria are not met, *prima facie* obviousness is not established, and Applicants are *not* required to show new or unanticipated results. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985).

B. The References Cited by the PTO Fail to Teach Each and Every Element of Claims 1-9

Claim 1 recites a method for the detection of a nucleic acid. In the method, a plurality of amplificates of a section of the nucleic acid are produced with two primers. One of the primers can bind to sequence A of one strand of the nucleic acid, and the other can bind to sequence C' which is essentially complementary to a sequence C which is located in the 3' direction from A and does not overlap A. The amplificates are produced in the presence of a probe with a binding sequence D which can bind to a third sequence (B) located between the sequences A and C or to the complement (B') thereof. The probe contains a reporter group and a quencher group, and the amplificates are produced using a polymerase having 5' nuclease activity. Significantly, the amplificates have a length of less than 75 nucleotides.

Surprisingly, the probe is capable of being degraded by the 5' nuclease activity of the polymerase thereby releasing the reporter group during amplification (*see* specification, for example, at page 22, line 24, through page 23, line 5, and at page 31, lines 1-10). Detection of the released reporter group can indicate the presence of the nucleic acid. Claims 2-9 depend from Claim 1. In Claim 4, the length of the amplificates is less than 61 nucleotides.

Neither Livak nor Western, alone or in any combination, teaches or suggests each and every element of the methods of Claims 1-9. For example, neither Livak nor Western, alone or in any combination, teaches or suggests that a probe containing a reporter group can be degraded by the 5' nuclease activity of a polymerase while the probe is bound to an amplificate having a length of less than 75 nucleotides.

Livak teaches a method for monitoring the progress of nucleic acid amplifications that relies on a nucleic acid polymerase having 5' to 3' exonuclease activity. As acknowledged by the PTO, Livak does not teach or suggest a method for the detection of a nucleic acid wherein amplificates having a length of less than 75 nucleotides are produced from a section of the nucleic acid.

Western teaches internal positive controls for nucleic acid amplification that are irrelevant to the invention recited in Claim 1. The PTO nevertheless asserts that Western, at col. 12-13, teaches an amplification product of 30 to 5000 nucleobases that is capable of hybridizing to a probe thereby rendering Claims 1-9 allegedly obvious. However, the PTO fails to explain how Western teaches or suggests that a probe containing a reporter group can be degraded by a polymerase while bound to an amplificate having a length of less than 75 nucleotides. The only method of detecting an amplification product in Western is gel electrophoresis (see Western at col. 30, lines 32-35). Furthermore, Western provides no teaching or suggestion that probe containing a reporter group can be degraded under such conditions. Western does not discuss the 5' nuclease activity of any polymerase, and, as acknowledged by the PTO, Western does not even teach or suggest a probe comprising a reporter group.

Nevertheless, the PTO asserts that it would have been obvious that "a reporter/quencher system would have been useful with the probe of Western et al. for identifying" a nucleic acid. However, the PTO provides no evidence to support the assertion that such a modification of the probe of Western would have been obvious. The PTO fails to provide any evidence in the cited references or in the art suggesting the use of a probe comprising a reporter group in the methods of Western.

Furthermore, the PTO has failed to indicate why one of skill in the art would have any reasonable expectation that the use of a probe comprising a reporter group would have any expectation of success in a method for the detection of a nucleic acid using amplificates less than 75 nucleotides in length. As acknowledged by the PTO, conventional detection methods using probes comprising reporter groups, such as the method of Livak, are limited to the use of much larger amplificates, typically of 150 nucleotides or more. When bound to a small amplificate, such as an amplificate having less than 75 nucleotides, the steric interactions of a primer, a polymerase and a probe are considerable.

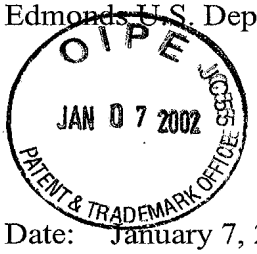
The PTO's assertion that the "size of the amplificate would have been irrelevant" as long as the amplificate can hybridize with the probe is inaccurate and inapposite. Hybridization of any amplificate to a probe is not sufficient. Rather, the amplificate should not only be capable of hybridizing to a probe, but the resulting amplificate and probe hybrid complex must have an appropriate size and form to permit proper polymerase binding and extension to efficiently degrade the probe and release the reporter group. The cited references provide no basis for expecting that a 75 nucleotide or smaller amplificate could form the required hybrid complex. By ignoring this feature of the claimed method, the PTO has failed to provide any expectation that one of skill in the art would be able to successfully detect a nucleic acid by combining a reporter group with the probe of Western.

Since neither Livak nor Western, alone or in any combination, teaches or suggests each and every element of Claims 1-9, and since the PTO has provides no expectation of success in practicing the asserted combination of Livak and Western, the PTO's asserted combination of Livak and Western is not sufficient to establish a *prima facie* case of obviousness Claims 1-9. Applicants therefore request that the rejections of Claims 1-9 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Applicants submit that Claims 1-9 satisfy all of the criteria for patentability and are in condition for allowance. An early indication of the same and passage of Claims 1-9 to issuance is therefore kindly solicited.

No fees in addition to the extension fee are believed due in connection with this response. However, the Commissioner is authorized to charge all required fees, fees under 37 CFR § 1.17 and all required extension of time fees, or credit any overpayment, to Pennie & Edmonds U.S. Deposit Account No. 16-1150.



Respectfully submitted,

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Rahul Pathak (Reg. No.)

For: Jennifer Gordon, (Reg. No. 30,753)
PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

Enclosure (Exhibits A & B)

EXHIBIT A
MARKED-UP VERSION OF AMENDED CLAIMS

1. (Three times amended) A method for the detection of a nucleic acid comprising the steps:

(a)- producing a plurality of amplificates of a section of the nucleic acid with the aid of two primers, one of which can bind to a first binding sequence (A) of one strand of the nucleic acid and the other can bind to a second binding sequence (C') which is essentially complementary to a sequence C which is located in the 3' direction from A and does not overlap A, in the presence of a probe with a binding sequence D which can bind to [the] a third sequence (B) located between the sequences A and C or to the complement (B') thereof, wherein this probe contains a reporter group and a quencher group, using a polymerase having 5' nuclease activity, and

(b)- detecting the nucleic acid by measuring a signal which is caused by the release of the reporter group, wherein the amplificates have a length of less than 75 nucleotides.

5. (Twice amended) The method of claim 1, wherein the probe is [labelled] labeled with a fluorescence quencher as well as with a fluorescent dye.